New chemotherapy agents and side effects patients present with to the AMU

Dr Toby Talbot
Consultant Clinical Oncologist
Royal Cornwall Hospital
Travel grants and honoraria from BMS, MSD, Roche, AMGEN, Novartis, Boehringer Ingleheim, Pfizer, GSK, IGEA medical systems and Varian medical systems
Background – a changing landscape

- Cancer incidence continues to rise globally
  - 50% of all humans alive today are expected to develop at least one cancer\(^1\)
  - More than 50% of patients with cancer are alive at ten years\(^1\)
  - Earlier detection of disease (screening, other investigations)
  - Survival gains are dramatic in many cancer types\(^1\)
    - \(^1\) CRUK
All Cancers Excluding Non-Melanoma Skin Cancer Plus Benign Brain Other CNS and Intracranial Tumours (C00-C97 (Excl. C44) D32-D33 D35.2-D35.4 D42-D43 D44.3-D44.5): 1979-2035

Observed and Projected Age-standardised Incidence Rates, by Sex, UK

Source: cruk.org/cancerstats

You are welcome to reuse this Cancer Research UK statistics content for your own work. Credit us as authors by referencing Cancer Research UK as the primary source. Suggested style: Cancer Research UK, full URL of the page, Accessed [month] [year].
Chemotherapy – a definition

- chemotherapy *noun*, *medicine* the treatment of a disease or disorder by means of drugs or other chemical compounds that are designed to destroy invading micro-organisms or specific areas of tissue, especially the treatment of cancer with cytotoxic drugs, as opposed to *radiotherapy*. *chemotherapeutic* *adj.*

* The Chambers Dictionary – chambers.co.uk
Figure 1. Key advances in the history of cancer chemotherapy

- **1900**: Arsenicals (1, 2)
- **1905**: Animal models (1–4)
- **1910**: Transplantable tumors (5–11)
- **1912**: Model development (7)
- **1915**: Nitrogen mustard in lymphomas (15–18)
- **1920**: 5-Fluorouracil (26)
- **1925**: Cancer Chemotherapy National Service Center
  - L1210 as primary screen (27–30)
- **1930**: Antifolates (22)
- **1935**: Antitumor antibiotics (23)
- **1940**: Thiopurines (24, 25)
- **1945**: Methotrexate in choriocarcinoma
- **1950**: Concept of cure
- **1955**: 1958
- **1960**: 1959
Chemotherapy timeline

- Special Virus Cancer Program (1964)
- Cure of ALL & Hodgkin's disease (1963–70)
- Vinca alkaloids (1963)
- Xenografts in nude mice (1975)
- Adjuvant chemotherapy (1968–75)
- Cure of testicular cancer (1976)
- National Cancer Act (1971)
- NCI investment in molecular biology (1984)
- Cancer mortality begins to decline (1990)
- First monoclonal antibody approved (1997)
- Imatinib (Gleevec) (1996)
- Cell culture systems (1990)
- Molecular profiling sequenced (2001)
- Genome sequenced (2002)
- Tyrosine kinase inhibitors (2005)
- Target specific screens (2007)
- Mortality decline accelerates (2007)

Figure 1 Continued.
“Chemotherapy” is the most widely used term by patients, relatives and healthcare providers

Systemic Anticancer Treatment – SACT is more accurate

- Cytotoxic agents
- Targeted agents (eg TKIs, monoclonal antibodies)
- Immunotherapy
- Hormone therapies
- Radionuclide therapies etc, etc, etc…
Virtually all cytotoxic drugs damage DNA in some way and inhibit cellular proliferation

- Rapidly proliferating cells most sensitive
- Cancer cells (on the whole) have rapid proliferation
- Many native cells also have rapid proliferation…
  - Hair, mucosa, skin, bone marrow etc…
  - Most conventional side effects can be explained by this fact
Cytotoxic familiarities

* Neutropenia with resultant opportunistic infections
  -> SEPSIS!

* Thrombocytopenia
  -> BLEEDING!

* GI mucosal +/- CTZ toxicity
  -> VOMITING!

* Direct end organ damage
  -> RENAL FAILURE/MULTI-ORGAN FAILURE!
New drugs, new problems

* Most targeted treatments are less (acutely) toxic than cytotoxic chemotherapy
  * Chronic toxicity is a problem – months or years of low grade side effects erode quality of life
  * EGFR TKI (Afatinib)

rash:
New drugs, new problems

- Notable exceptions with VEGF inhibitors
  - Bevacizumab (Avastin), Sunitinib, Pazopanib etc
- Acute hypertensive crises
- Haemorrhagic events
- Bowel perforation
MTOR inhibitors such as Everolimus can cause acute, severe pneumonitis
For decades it has been recognised that there is an interaction between the immune system and cancers.
For decades, attempts have been made to exploit this interaction in a therapeutic way

- Trial after trial of disappointing results
- Occasional outstanding benefits in individuals but idiosyncratic
- Some tumours more “immunogenic” than others (melanoma, renal cell, lung cancer)
In 2010/2011 Ipilimumab – a humanised monoclonal antibody against CTLA4 (an immune checkpoint) showed an overall survival gain in melanoma for the first time ever.
Ipilimumab

Ipilimumab + DTIC versus Placebo + DTIC
HR (95% CI) 0.72 (0.59–0.87)
Median OS 11.2 vs 9.1 months
P value 0.0009

Table: Estimated Survival Rate

<table>
<thead>
<tr>
<th>Estimated Survival Rate</th>
<th>1 Year</th>
<th>2 Year</th>
<th>3 Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab + DTIC n=250</td>
<td>47.3</td>
<td>28.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Placebo + DTIC n=252</td>
<td>36.3</td>
<td>17.9</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*3-year survival was a post-hoc analysis
We are now in the PD1/PDL1 era

- Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab etc – more are coming...
- Generally less acutely toxic than CTLA4 inhibitors
- Many more indications, longer exposure
- Many more checkpoint and co-stimulating targets under investigation...
Immunotherapy

Activating receptors

CD28
OX40
GITR
CD137
CD27
HVEM

Inhibitory receptors

CTLA-4
PD-1
TIM-3
BTLA
VISTA
LAG-3

Agonistic antibodies

T-cell stimulation

Blocking antibodies

www.nature.com
Massive survival gains now being seen in melanoma, lung cancer, bladder cancer, kidney cancer etc

It is predicted that by the year 2022 more than 50% of cancer patients will be exposed to an immunotherapy agent at some point in their journey

The way we treat advanced cancer is changing!
Immunotherapy – implications for acute medicine

- Immunotherapy acts to enhance anti-tumour immune response
  - Autoimmune phenomena can result
  - Severe/life threatening toxicity is recognised
  - Timing of toxicity is idiosyncratic
  - Toxicity can be easy to miss or mistaken for other pathology
AEs associated with immuno-oncology (IO) therapies\textsuperscript{1,2}

- Pneumonitis
- Colitis
- Hepatitis
- Nephritis and renal dysfunction
- Endocrinopathies
- Rash
- Other

\textsuperscript{1} Nivolumab (OPDIVO) Summary of Product Characteristics; \textsuperscript{2} Ipilimumab (YERVOY) Summary of Product Characteristics
Toxicity kinetics*

*General AE profile with ipilimumab: AEs exhibited a characteristic pattern in the timing of their occurrence as shown in a pooled analysis of 325 patients treated with 10 mg/kg ipilimumab once every 3 weeks for four times
Toxicity management – general rules

• Early identification is the key to success!
  – Unexplained (even vague) symptoms need to be viewed with suspicion

If confirmed immune-related side effect then follow relevant algorithm – and advice as stated within the SmPC

Depending on severity, withhold treatment (most can restart on resolution of AE) or permanently discontinue treatment

Immunosuppress – steroids, other immunosuppression

• Get a team of specialists together!

1. Nivolumab (OPDIVO) Summary of Product Characteristics
GI toxicity/colitis

GI toxicity/colitis: the dominant toxicity from CTLA4i

- Early study with ipilimumab saw 27% patients with diarrhoea and 8% diagnosed with colitis in the ipilimumab 3 mg/kg monotherapy group*

Seems to be less common with single agent PD1i

- Increased awareness now (based on personal experience)

More common with combination CTLA4/PD1i

- Increased awareness now (based on personal experience)

Based on patients who received either ipilimumab 3 mg/kg monotherapy (n=131) or ipilimumab 3 mg/kg in combination with gp100 (n=380) in a Phase 3 study of advanced (unresectable or metastatic) melanoma (MDX010-20)

Colitis case
Colitis case

- 74-year-old male, melanoma, presented with stage IV disease – axilla and gallbladder
  - Axillary dissection and laparoscopic cholecystectomy
  - Surveillance imaging

<table>
<thead>
<tr>
<th>Date</th>
<th>Event/Condition</th>
</tr>
</thead>
</table>
| April 2010                | • BRAF positive  
                          • Multiple liver metastases                                                  |
| MEK inhibitor trial at RMH| • Initial response then PD                                                      |
| Ipilimumab through Named Patient Programme (NPP) scheme | • Four cycles complete                                                        |
| Day after last infusion   | • Abdominal pain and diarrhoea +++                                               |

The AEs focused on in case studies in this presentation were selected as they are the most common seen in my view and practice. This case was chosen because it represents a good case to illustrate managing AEs. This case cannot be seen to represent the typical response of all patients to ipilimumab. Please refer to the summary of product characteristics (SPC) for full information before initiation of ipilimumab.
Colitis – CT

All scans and images provided by the physician
Colitis – rectal biopsy
Colitis – management

Admitted (reluctantly…)

- Early involvement of GI team
- Colonoscopy and biopsy confirms severe colitis
- Methylprednisolone 1 g IV od for 3 days
- Switch to oral prednisolone 60 mg – very slow taper over 14 weeks due to re-emergent symptoms on reduction
- Significant steroid related side effects (myopathy, chushingoid facies, etc.)
Pre-treatment

All scans and images provided by the physician
8 weeks post ipilimumab
3 months

All scans and images provided by the physician
6 months

All scans and images provided by the physician
6 years!!!
Endocrinopathies

Thyroid and pituitary toxicity is common with PD1i or CTLA4i monotherapy*, adrenal less so¹⁻³

- Endocrinopathies more frequent with PD1i/CTLA4i combination therapy than PD1i or CTLA4i monotherapy¹
  - Mainly thyroid
  - Hypophysitis more common with CTLA4i monotherapy than PD1i monotherapy¹

Of all immune side effects these are the easiest to miss!**

- Regular monitoring (TFT, cortisol, sex hormones) essential

---

*Common defined as ≥ 1/100 to < 1/10. **Speaker’s opinion
Hypophysitis case

- 61-year-old male, melanoma stage III (axillary nodes) August 2015
  - Axillary dissection, no adjuvant therapy, on surveillance imaging

April 2016

- Mediastinal nodes
- Low-volume lung metastases

Treated with ipilimumab

- Four cycles completed without difficulty

3 weeks after last cycle developed fatigue/malaise and frontal headaches

- GP telephoned: ?brain metastases
- Urgent bloods and MRI brain with pituitary views

The AEs focused on in case studies in this presentation were selected as they are the most common seen in my view and practice. This case was chosen because it represents a good case to illustrate managing AEs. This case cannot be seen to represent the typical response of all patients to ipilimumab. Please refer to the summary of product characteristics (SPC) for full information before initiation of ipilimumab.
Pituitary MRI

All scans and images provided by the physician
Hypophysitis case – bloods

- TSH 0.22 (ref 0.27–4.2)
- Free T4 8.0 (ref 12–22)
- Cortisol 65 (ref 170–700)
- Testosterone 1.9 (ref 6.7–25.8)
- LH 3.1 (ref 1.5–25.8)
- FSH 5.4 (ref 1.7–8.6)
Hypophysitis – management

- Patient admitted under endocrinology/oncology shared care
- Commenced thyroxine and testosterone
- Prednisolone 60 mg od with plan to taper 10 mg weekly
  - May need long-term steroid replacement
  - Under ongoing endocrine review
  - Endocrine dysfunction likely to be long term, but some recovery possible
Hepatic toxicity

Hepatic toxicity uncommon* with PD1i and CTLA4i monotherapy¹,²

- Much more common with combination ipilimumab and nivolumab¹,³
- Usually asymptomatic – detected on routine bloods

Usually fully reversible¹ and may not recur on rechallenge

*Defined as ≥ 1/1,000 to < 1/100
Hepatitis case

- 27-year-old female, metastatic melanoma in pregnancy August 2009
  - Nodal disease, resected, surveillance

- June 2011
  - Internal pelvic nodes resected

- March 2012
  - Para-aortic nodes and serosal small bowel deposits resected
  - BRAF negative, NRAS positive

- September 2014
  - Widespread nodal disease
  - NEMO study, randomised to dacarbazine
  - PD
  - Ipilimumab x4 cycles
  - No toxicity but PD
  - Nivolumab within CheckMate 172 study

The AEs focused on in case studies in this presentation were selected as they are the most common seen in my view and practice. This case was chosen because it represents a good case to illustrate managing AEs. This case cannot be seen to represent the typical response of all patients to ipilimumab or nivolumab. Please refer to the summary of product characteristics (SPC) for full information before initiation of ipilimumab or nivolumab.
Hepatitis case

- No symptomatic side effects from nivolumab, partial response on CT, treatment continued
- Routine bloods detected rise in ALT in August 2015
  - Treatment interrupted, as per trial protocol

<table>
<thead>
<tr>
<th>Date</th>
<th>24/07</th>
<th>07/08</th>
<th>11/08</th>
<th>20/08</th>
<th>21/08</th>
<th>22/08</th>
<th>24/08</th>
<th>26/08</th>
<th>28/08</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>17</td>
<td>126</td>
<td>77</td>
<td>264</td>
<td>292</td>
<td>199</td>
<td>110</td>
<td>96</td>
<td>67</td>
</tr>
</tbody>
</table>

Steroids – prednisolone 60 mg
Hepatitis case

- Ten-week break from nivolumab, but remained on study
- LFTs resolved to grade 0
  - Nivolumab restarted – LFTs watched very carefully
- No recurrence of ALT rise
  - Ongoing response, excellent tolerance
  - Remains on treatment; over 18 months in total
Pneumonitis

• Fairly common* with PD1i, less so with CTLA4i\(^1\)–\(^3\)
• Easy to miss or confuse with other pathology
  – Patients often admitted under medics, treated for infection
• More frequent and more problematic in lung cancer\(^4\)

*Common defined as ≥ 1/100 to < 1/10
Pneumonitis case

- 67-year-old male patient, uveal melanoma
  - Enucleation September 2010 – unfavourable cytogenetics
  - Surveillance imaging

January 2016:
- breathlessness, cough, fever
- Admitted: ?pneumonia
- Multiple lung, liver and renal metastases
- Attempted biopsy x2 – non-diagnostic

Commenced pembrolizumab
- Nine-week scan good partial response, well tolerated
- After cycle 12 became breathless: ?disease progression

The AEs focused on in case studies in this presentation were selected as they are the most common seen in my view and practice. This case was chosen because it represents a good case to illustrate managing AEs. This case cannot be seen to represent the typical response of all patients to pembrolizumab. Please refer to the summary of product characteristics (SPC) for full information before initiation of pembrolizumab.
Pneumonitis on CTPA

All scans and images provided by the physician
Pneumonitis management

- Admitted, high-flow oxygen and antibiotics
  - Respiratory opinion
  - Methylprednisolone 500 mg IV od for 3 days
  - Switch to prednisolone 60 mg od with plan to taper 10 mg/week
- Good clinical response within 48 hours
  - Unlikely to rechallenge with pembrolizumab, given high-grade toxicity
Main impact on acute medical services over next few years will be from immunotherapy
  * Increased use in increased indications
  * Recognition of side effects is crucial!
    * Need good communication links with oncology teams
  * Treatment is STEROIDS!!!
    * High doses methylprednisolone will buy time (I use 500mg iv od for three days, minimum...)
    * Call oncologist involved for advice – may need complex immunosuppression if severe or steroid refractory
Conclusions

* End organ effects will need specialist physicians to become involved
* It is very likely that we will see totally new and unexpected emergent toxicities from novel agents

* Collaborative working is key to success!
  * Acute oncology needs to be fully implemented everywhere – and kept up to date.
Thanks!

* That’s it! Any questions?

  tobytalbot@nhs.net